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Annex A. Comparative Positioning of the OncoBalance Model Relative to Current Oncology Models

This annex compares the OncoBalance Model with major current oncology model families and explains why its main value may lie in **integration rather than substitution**. Current oncology already benefits from clinically useful biomarkers and predictive models, but many of them remain one-dimensional, treatment-specific, or weakly integrated across genomic, epigenetic, repair, immune, and longitudinal monitoring layers. The OncoBalance framework is positioned as a systems-level architecture that can absorb the strengths of these existing tools while reducing fragmentation in biological interpretation. [file:150][web:148][web:198][web:201]

1. Comparative context

Modern oncology commonly relies on several model families: single biomarkers such as PD-L1, TMB, MSI/dMMR, and HRD; transcriptomic prognostic signatures; clinicogenomic nomograms; and liquid-biopsy monitoring approaches. Each of these has demonstrated clinical or translational value, yet each typically emphasizes only one slice of tumor biology or one moment in the disease course. Reviews of precision-oncology biomarkers and multi-omics approaches increasingly stress that single markers often fail to capture the full complexity of tumor behavior and treatment response. [web:148][web:199][web:201]

The OncoBalance Model differs because it is designed to represent malignant transition as the result of a balance between oncogenic burden and biological protection. Instead of treating mutational burden, gene expression, epigenetic disruption, DNA repair, and immune activity as disconnected evidence streams, it places them into a single mathematically coherent structure. [file:150]

2. Comparison with current model families

2.1 Single-biomarker frameworks

Current clinical practice frequently uses isolated biomarkers such as PD-L1, TMB, MSI/dMMR, or HRD to support treatment selection or biological classification. These markers are valuable because they are

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assay-specific, clinically familiar, and often actionable, but their performance is limited by context dependence and incomplete biological coverage. For example, recent literature on immunotherapy biomarkers emphasizes that PD-L1, TMB, and MSI each provide meaningful but only partial information about response probability. [web:134][web:135][web:148][web:201]

In contrast, OncoBalance does not treat any single biomarker as a complete representation of malignant risk. It treats TMB as one contributor to oncogenic burden, repair deficiency as a modifier of system protection, and immune activity as a counterbalancing force. This integrated design is especially useful in settings where no single biomarker is sufficiently discriminative. [file:150]

2.2 Transcriptomic and prognostic signature models

Many current cancer models are built from gene-expression signatures or machine-learning-based prognostic panels. In prostate cancer, for example, several multi-gene signatures and nomograms have shown predictive utility for progression-free survival and risk stratification. These models can perform well, but they are typically optimized for endpoint prediction rather than for explicit mechanistic balance across multiple biological protection and damage axes. [web:203][web:205][web:207][web:209]

OncoBalance is compatible with these models because transcriptomic signatures can be incorporated directly into the E_{gene} term or, depending on design, also contribute to repair and immune subcomponents. This means the framework can preserve the predictive value of existing signatures while embedding them inside a more interpretable systems architecture. [file:150]

2.3 Immunotherapy biomarker models

Immunotherapy prediction is increasingly recognized as a multi-factorial problem. Current literature notes the limitations of using PD-L1, TMB, or MSI in isolation and points toward integrated multi-omics and AI-enabled biomarker frameworks as better strategies for predicting immune checkpoint inhibitor response. The central message across recent reviews is that durable response depends not only on antigenicity but also on immune state, tumor microenvironment, and dynamic tumor evolution. [web:199][web:200][web:201][web:204]

This logic is already embedded in OncoBalance. Because the framework explicitly couples oncogenic burden with immune protection and repair capacity, it is well suited to function as an integration layer

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for immunotherapy biomarker ecosystems. It therefore complements, rather than competes with, current response-prediction efforts. [file:150]

2.4 Liquid-biopsy and longitudinal monitoring models

Liquid biopsy has become increasingly important for real-time disease monitoring, immunotherapy follow-up, early response assessment, and detection of tumor evolution. Reviews on ctDNA-based monitoring show that liquid biopsy can capture tumor burden, mutational evolution, microsatellite instability, and treatment response in ways that are difficult to obtain from static tissue sampling. However, the literature also emphasizes that single liquid-biopsy markers often lack enough sensitivity or interpretive completeness when used alone. [web:202][web:204][web:206][web:208]

The OncoBalance Model is naturally compatible with this domain because serial ctDNA, methylation, and immune-associated markers can be integrated as time-varying inputs to H_q , I_{immune} , and ΔB . This gives the framework a clear role as a mathematical shell for longitudinal synthesis rather than as a replacement for the underlying assays. [file:150]

3. Comparative table

Model family	Main current use	Main strength	Main limitation	Position of OncoBalance	Integration benefit
Single biomarkers (PD-L1, TMB, MSI/dMMR, HRD)	Treatment selection, stratification, biological classification [web:134][web:135][web:148]	Assay-specific, clinically familiar, often actionable [web:148]	One-dimensional, context-dependent, incomplete systems view [web:201]	Uses each biomarker as one structured element inside the balance framework [file:150]	Preserves validated biomarkers while reducing isolated interpretation [file:150][web:201]

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Gene-expression signatures and prognostic panels	Prognosis, recurrence risk, progression prediction [web:203][web:205][web:207]	Good predictive performance in defined cohorts [web:203][web:207]	Often endpoint-specific and not explicitly mechanistic [web:205]	Embeds transcriptomic signatures into oncogenic, repair, or immune components [file:150]	Retains predictive value while improving biological interpretability [file:150]
Clinicogenomic nomograms	Risk stratification and decision support [web:203][web:209]	Easy clinical translation, combines clinicopathologic and molecular data [web:203]	May underrepresent molecular interaction structure [web:209]	Can sit above nomograms as a biological synthesis layer [file:150]	Adds systems-level context to existing decision tools [file:150]
Immunotherapy biomarker models	Predicting ICI response and resistance [web:199][web:201][web:204]	Direct therapeutic relevance [web:199]	Fragmented across PD-L1, TMB, MSI, TILs, and TME features [web:201]	Couples antigenic burden, repair status, and immune activity in one score [file:150]	Better joint interpretation of tumor-immune interaction [file:150][web:201]
Liquid-biopsy monitoring models	Real-time response assessment, relapse monitoring, tumor evolution [web:202][web:206][web:208]	Dynamic, minimally invasive, suitable for repeated measurement [web:206]	Sensitivity variability and fragmented single-marker interpretation [web:202][web:208]	Provides a structured longitudinal container through B and ΔB [file:150]	Converts serial molecular signals into a coherent instability trajectory [file:150][web:206]

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Multi-omics integrated AI models	Systems-level prediction and biomarker fusion [web:198][web:200][web:201]	Strong potential to capture biological complexity [web:198][web:201]	Often difficult to interpret clinically and operationalize transparently [web:200]	Offers a more explicit and interpretable balance-based architecture [file:150]	Enables integration without losing mechanistic readability [file:150][web:198]
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4. Benefits of integration with current models

4.1 More complete biological representation

The main benefit of integrating OncoBalance with current models is that it allows multiple partial truths to be interpreted together. TMB may reflect mutational burden, PD-L1 may reflect one axis of immune escape, methylation may reflect regulatory instability, and transcriptomic signatures may reflect active oncogenic programs; OncoBalance provides a structure in which these signals can be combined rather than compared as competing explanations. [file:150][web:148][web:201]

4.2 Better interpretability across data modalities

A recurring challenge in modern oncology is that clinically relevant information is distributed across separate assays and analytic frameworks. OncoBalance reduces this fragmentation by translating heterogeneous signals into a common balance architecture: numerator-dominant variables reflect destabilizing burden, and denominator-dominant variables reflect repair and immune protection. This creates a coherent biological narrative that can support translational interpretation. [file:150]

4.3 Greater compatibility with precision oncology workflows

A practical advantage of the model is that it does not require current biomarkers or workflows to be abandoned. Existing assays for PD-L1, TMB, MSI/dMMR, HRD, RNA signatures, and ctDNA can remain in place and serve as validated inputs to the model. This lowers the implementation barrier because integration can occur incrementally on top of present-day precision-oncology practice. [file:150][web:148][web:206]

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4.4 Improved longitudinal interpretation

Many existing tools provide powerful snapshots but less coherent tracking over time. By combining static burden and protection terms with the temporal derivative ΔB , OncoBalance has the potential to synthesize serial liquid-biopsy and molecular-monitoring data into a dynamic instability profile. This is especially important in recurrence surveillance, molecular residual disease monitoring, and treatment-response tracking. [file:150][web:202][web:206][web:208]

4.5 Clearer assessment of incremental value

Because the model can be placed on top of existing biomarker frameworks, its value can be evaluated rigorously through incremental-performance analysis rather than rhetorical replacement claims. This is scientifically stronger: the relevant question is not whether OncoBalance can replace current tools, but whether it improves discrimination, calibration, longitudinal interpretation, or biological coherence when used jointly with them. [file:150]

5. Annex conclusion

The OncoBalance Model should be presented as a complementary and integrative framework rather than as a substitute for current oncology models. Its distinguishing contribution is not that it invalidates existing biomarkers or signatures, but that it offers a mathematically explicit way to combine them into a balance-based representation of malignant risk and system instability. [file:150][web:148][web:201]

This positioning is scientifically stronger and more clinically realistic. If validated properly, OncoBalance could serve as an organizing layer that preserves the strengths of current biomarkers, transcriptomic signatures, immunotherapy predictors, and liquid-biopsy tools while enabling a more unified interpretation of cancer biology and progression. [file:150][web:198][web:206]

phenomenon.[cite:49][cite:57][cite:62]

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